PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DOTAREM® 0,5 mmol/mL Solution for injection

DOTAREM® PREFILLED SYRINGES 0,5 mmol/mL Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Per 100 mL of solution:

Gadoteric acid* 27,932 g

corresponding to DOTA 20,246 g

corresponding to gadolinium oxide 9,062 g

*Gadoteric acid: 1,4,7,10-tetra-azacyclododecane-N,N',N",N"'-tetra-acetic acid gadolinium complex

Contrast agent concentration: 0,5 mmol/mL

For the full list of excipients, see section 6.1

Sugar free.

3. PHARMACEUTICAL FORM

Solution for injection in vials and prefilled syringes.

A clear, colourless to yellow solution.

Osmolality: 1350 mOsm/kg

Viscosity at 20 ºC: 3,2 mPa.s

Viscosity at 37 ºC: 2,0 mPa.s

pH: 6,5 – 8,0

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DOTAREM is for diagnostic use only.

DOTAREM should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI).

Adult population

Enhancement of contrast in Magnetic Resonance Imaging (MRI).

Encephalic and spinal MRI: Detection of brain tumours, tumours of the spine and the surrounding tissue, intervertebral disk prolapse, infectious diseases.

Whole body MRI including imaging for renal, cardiac, uterine, ovarian, breast, abdominal (primary and secondary liver tumours) and osteo-articular pathologies (bone and soft tissue tumours, synovial diseases).

Angiography.

Paediatric population (0-18 years)

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4.2 Posology and method of administration

Posology

The lowest dose that provides sufficient enhancement for diagnostic purposes should be used. The dose should be calculated based on the patient's body weight and should not exceed the recommended dose per kilogram of body weight detailed in this section.

Adults including the elderly

Encephalic and Spinal MRI. In most cases the recommended dose is 0,1 mmol/kg, i.e. 0,2 ml/kg which is sufficient to provide diagnostically adequate contrast. If a strong clinical suspicion of a lesion persists despite a normal MRI examination, a further injection of 0,2 mmol/kg, i.e. 0,4 ml/kg within 30 minutes, may improve tumour characterisation and facilitate therapeutic decision making.

Whole body MRI and Angiography. The administration of 0,1 mmol/kg, i.e. 0,2 ml/kg is recommended to provide diagnostically adequate contrast.

Angiography: In exceptional circumstances (e.g. failure to gain satisfactory images of an extensive vascular territory) administration of a second consecutive injection of 0,1 mmol/kg, i.e. 0,2 ml/kg may be justified. However, if the use of 2 consecutive doses of DOTAREM is anticipated prior to commencing angiography of certain regions (such as leg arteries or lungs), use of 0,05 mmol/kg (i.e. 0,1 ml/kg) for each dose may be of benefit, depending on the imaging equipment available.

Special populations

Impaired renal function

The adult dose applies to patients with mild to moderate renal impairment (GFR ≥ 30 ml/min/1.73m^2).

DOTAREM should only be used in patients with severe renal impairment (GFR < 30 ml/min/1.73m^2) and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI (see section 4.4). If it is necessary to use DOTAREM, the dose should not exceed 0,1 mmol/kg body weight.

More than one dose should not be used during a scan. Because of the lack of information on repeated administration, DOTAREM injections should not be repeated unless the interval between injections is at least 7 days.

Elderly (aged 65 years and above)

No dosage adjustment is considered necessary. Caution should be exercised in elderly patients (see section 4.4).

Impaired hepatic function

The adult dose applies to these patients. Caution is recommended, especially in the case of perioperative liver transplantation period.

Paediatric population (0-18 years)

MRI of brain and spine / whole-body MRI: the recommended and maximum dose of DOTAREM is 0,1 mmol/kg, i.e. 0,2 ml/kg body weight. More than one dose should not be used during a scan.

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, DOTAREM should only be used in these patients after careful consideration, at a dose

not exceeding 0,1 mmol/kg, i.e. 0,2 ml/kg body weight. Because of the lack of information on repeated administration, DOTAREM injections should not be repeated unless the interval between injections is at least 7 days.

Angiography: Gadoteric acid is not recommended for angiography in children under 18 years of age due to insufficient data on its efficacy and safety in this indication.

Method of administration

The product is intended for intravenous administration only.

Intravascular administration of contrast media should, if possible, be done with the patient lying down. After the administration, the patient should be kept under observation for at least half an hour, since experience shows that the majority of undesirable effects occur within this time.

Paediatric population (0-18 years)

Depending on the amount of DOTAREM to be given to the child, it is preferable to use DOTAREM vials with a single use syringe of a volume adapted to this amount in order to have a better precision of the injected volume.

In neonates and infants, the required dose should be administered by hand.

4.3 Contraindications

Hypersensitivity to gadoteric acid, to meglumine or to any medicine containing gadolinium.

4.4 Special warnings and precautions for use

Administer only by strict intravenous injection. In the event of extravasation, local intolerance reactions can occur, which require conventional local treatment.

DOTAREM must not be administered by subarachnoid (or epidural) injections.

The usual precaution measures for MRI examination should be taken, such as exclusion of patients with pacemakers, ferromagnetic vascular clips, infusion pumps, nerve stimulators, cochlear implants, or suspected intracorporal metallic foreign bodies, particularly in the eye.

Hypersensitivity

- Hypersensitivity reactions can occur during use of DOTAREM, including life threatening (see section 4.8). Hypersensitivity reactions may be either allergic (described as anaphylactic reactions when serious) or non-allergic. They can be either immediate (less than 60 minutes) or delayed (up to 7 days). Anaphylactic reactions occur immediately and can be fatal. They are independent of the dose, can occur after even the first dose of the product, and are often unpredictable.
- There is always a risk of hypersensitivity regardless of the dose injected.
- Patients who have experienced a reaction during previous administration of a gadolinium-containing MRI contrast agent present an increased risk of experiencing another reaction on subsequent administration of the same product, or possibly other products, and are therefore considered to be at high risk.
- The injection of DOTAREM may aggravate symptoms in patients with asthma. In patients with uncontrolled asthma unbalanced by the treatment, the decision to use DOTAREM must be made after careful evaluation of the risk/benefit ratio.
- Hypersensitivity reactions can be aggravated in patients on beta-blockers, and particularly in the presence of bronchial asthma. These patients may be refractory to standard treatment of hypersensitivity reactions with beta-agonists (see section 4.5).
- Before any contrast medium is injected, the patient should be questioned for a history of allergy (e.g. seafood allergy, hay fever, hives), sensitivity to contrast media and bronchial asthma as the reported incidence of adverse reactions to contrast media is higher in patients with these conditions. In such patients the decision must be made after careful consideration of the risk benefit ratio and premedication with antihistamines and/or glucocorticoids may be considered.

- During the MRI, supervision by a medical practitioner is necessary. If hypersensitivity reactions occur, administration of the contrast media must be discontinued immediately and, if necessary, specific therapy instituted. A venous access should thus be kept during the entire examination. To permit immediate emergency countermeasures, appropriate medicines (e.g. epinephrine and antihistamines), an endotracheal tube and a respirator should be ready at hand.

Impaired renal function

Prior to administration of DOTAREM, it is recommended that all patients are screened for renal dysfunction by obtaining appropriate laboratory tests.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR < 30 ml/min/1.73m^2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. As there is a possibility that NSF may occur with DOTAREM, it should therefore only be used in patients with severe renal impairment and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI.

Haemodialysis shortly after DOTAREM administration may be useful at removing gadoteric acid from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

Elderly

As the renal clearance of DOTAREM may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

Paediatric population

Neonates and infants

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, DOTAREM should only be used in these patients after careful consideration.

CNS disorders

Like with other gadolinium containing contrast agents, special precaution is necessary in patients with a low threshold for seizures. Precautionary measures should be taken, e.g. close monitoring. All equipment and medicines necessary to counter convulsions, which may occur, must be made ready for use beforehand.

4.5 Interaction with other medicines and other forms of interaction

No interactions have been reported with other medicines. Formal medicine interaction studies have not been carried out.

Concomitant medicines to be taken into account

Beta-blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists: these medicines decrease the efficacy of the mechanisms of cardiovascular compensation for blood pressure disorders: the radiologist must be informed before injection of gadolinium complexes, and resuscitation equipment must be at hand (see section 4.4).

4.6 Fertility, Pregnancy and Lactation

Although no teratogenic effects have been observed in animals to date, the safety of DOTAREM in human pregnancy and lactating women has not been demonstrated (see section 5.3).

Pregnancy

DOTAREM should not be used during pregnancy unless the clinical condition of the woman requires use of DOTAREM.

Breastfeeding

Gadolinium containing contrast agents are excreted into breast milk in very small amounts (see section 5.3). At clinical doses, no effects on the infant are anticipated due to the small amount excreted in milk and poor absorption from the gut. Continuing or discontinuing breastfeeding for a period of 24 hours after administration of DOTAREM, should be at the discretion of the doctor and lactating mother.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Ambulant patients while driving vehicles or operating machinery should take into account that nausea may incidentally occur.

4.8 Undesirable effects

a. Summary of the safety profile

Side effects in association with the use of DOTAREM are usually mild to moderate in intensity and transient in nature. A sensation of heat, cold and/or pain at the injection site, nausea and headache are the most frequently observed reactions.

b. Tabulated summary of adverse reactions

During clinical trials nausea, headache, injection site reactions, feeling cold, hypotension, somnolence, dizziness, feeling hot, burning sensation, rash, asthenia, dysgeusia and hypertension were the most frequent, uncommonly observed (≥ 1/1000 to < 1/100) related adverse events.

Since post-marketing, the most commonly reported adverse reactions following administration of DOTAREM have been nausea, vomiting, pruritus and hypersensitivity reactions.

The adverse reactions are listed in the table below by SOC (System Organ Class) and by frequency with the following guidelines: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). The data presented are from clinical trials involving 2822 patients when available, or from a pool of observational studies involving 185,500 patients.

System Organ Class	**Frequency: adverse reaction**
Immune system disorders	Uncommon: hypersensitivity Very rare: anaphylactic reaction, anaphylactoid reaction
Psychiatric disorders	Rare: anxiety Very rare: agitation
Nervous system disorders	Uncommon: headache, dysgeusia, dizziness, somnolence, paraesthesia (including burning sensation) Rare: presyncope Very rare: coma, convulsion, syncope, tremor, parosmia
Eye disorders	Rare: eyelid oedema Very rare: conjunctivitis, ocular hyperaemia, vision blurred, lacrimation increased
Cardiac disorders	Rare: palpitations Very rare: tachycardia, cardiac arrest, arrhythmia, bradycardia
Vascular disorders	Uncommon: hypotension, hypertension, Very rare: pallor, vasodilatation

Respiratory, thoracic and mediastinal disorders	Rare: sneezing Very rare: cough, dyspnoea, nasal congestion, respiratory arrest, bronchospasm, laryngospasm, pharyngeal oedema, dry throat, pulmonary oedema
Gastrointestinal disorders	Uncommon: nausea Very rare: diarrhoea, abdominal pain Rare: vomiting, diarrhoea, salivary hypersecretion
Skin and subcutaneous tissue disorders	Uncommon: rash Rare: urticaria, pruritus, hyperhidrosis Very rare: erythema, angioedema, eczema Not known: nephrogenic systemic fibrosis
Musculoskeletal and connective tissue disorders	Very rare: muscle cramps, muscular weakness, back pain
General disorders and administration site conditions	Uncommon: feeling hot, feeling cold, asthenia, injection site reactions (extravasation, pain, discomfort, oedema, inflammation, coldness) Rare: chest pain, chills Very rare: malaise, chest discomfort, pyrexia, face oedema, injection site necrosis (in case of extravasation), phlebitis superficial
Investigations	Very rare: decreased oxygen saturation

c. Description of selected adverse reactions

In hypersensitivity reactions, the reactions most frequently observed are skin reactions, which can be localised, extended or generalised.

These reactions occur most often immediately (during the injection or within one hour after the start of injection) or sometimes delayed (one hour to several days after injection), presenting as skin reactions in this case.

Immediate reactions include one or more effects, which appear simultaneously or sequentially, which are most often cutaneous, respiratory, gastrointestinal, articular and/or cardiovascular reactions.

Each sign may be a warning sign of a starting shock and goes very rarely to death.

Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with DOTAREM, most of which were in patients co-administered other gadolinium containing contrast agents (see section 4.4).

d. Paediatric population

Adverse reaction in Children

Safety of paediatric patients was considered in clinical trials and post-marketing studies. As compared to adult, the safety profile of DOTAREM did not show any specificity in children. Most of the reactions are gastrointestinal symptoms or signs of hypersensitivity.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc-org) found on SAHPRA website:

SAHPRA: https://www.sahpra.org.za/Publications/Index/8.

Guerbet South Africa (Pty) Ltd: pharmacovigilance.za@guerbet.com

4.9 Overdose

See Undesirable effects (section 4.8). Treatment is symptomatic and supportive.

DOTAREM can be removed by haemodialysis. However, there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A28 Contrast media

Pharmacotherapeutic group: paramagnetic contrast media for MRI, ATC code: V08 CA02.

Gadoteric acid has paramagnetic properties which increase contrast enhancement in magnetic resonance images. It has no specific pharmacodynamic activity and is biologically inert.

Gadoteric acid is formed by complexing of the paramagnetic ion, gadolinium with 1,4,7,10-tetra-azacyclododecane-N,N',N",N"'-tetra-acetic acid (DOTA). The presence of 7 unpaired electrons of the gadolinium ion Gd^{3+}, attributes to the string paramagnetic properties, with a shortening of the T_1 longitudinal relaxation time. This results in an increased signal intensity in T_1-weighted sequences and reduced signal intensity in T_2-weighted sequences in the magnetic resonance imaging.

5.2 Pharmacokinetic properties

Pharmacokinetic studies indicate that DOTAREM is distributed in the extracellular fluids. It is not bound to plasma albumin.

In patients with normal renal function, the plasma half-life is approximately 90 minutes. It is eliminated by glomerular filtration in unchanged form.

Plasma clearance is delayed in patients with impaired renal function.

A small amount of gadoteric acid is excreted in breast milk and crosses the placenta.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans, based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, or toxicity to reproduction.

In acute toxicity studies of intravenous gadoteric acid in mice and rats, adverse effects (seizures, transient respiratory disorders) were only reported at doses much higher than those used in man.

Administration of gadoteric acid at daily doses of up to 15 times the recommended dose in clinical practice and for 28 days did not induce any marked effect apart from reversible vacuolization of renal proximal tubular cells.

Animal studies showed negligible (less than 1% of the administered dose) secretion of gadoteric acid in maternal milk.

No teratogenic effect was demonstrated in rats and rabbits.

No mutagenic effect was demonstrated on the reagent systems used.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Meglumine, water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, DOTAREM must not be mixed with other medicines.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Store at or below 30 ºC.

Prefilled syringes: Do not freeze.

6.5 Nature and contents of container

DOTAREM sterile solution for injection is available in clear glass vials containing 5 ml, 10 ml, 15 ml, 20 ml, 60 ml and 100 ml and DOTAREM PREFILLED SYRINGES in 10 ml, 15 ml and 20 ml plastic prefilled syringes.

DOTAREM sterile solution for injection and DOTAREM PREFILLED SYRINGES are sold as single units or as 10 units per pack.

Not all pack sizes are marketed at any one time.

6.6 Special precautions for disposal and other handling

Vials: Prepare a syringe with a needle. Remove the plastic disk. After cleaning the stopper with a pad soaked in alcohol, puncture the stopper with the needle. Withdraw the quantity of product required for the examination and inject it intravenously.

The peel-off tracking label on the vials should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded. If electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record.

Any unused product or waste material should be disposed of in accordance with local requirements.

Prefilled syringes: Screw the piston onto the syringe and intravenously inject the quantity of the product required for the examination.

The peel-off tracking label on the syringes should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded. If electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Guerbet South Africa (Pty) Ltd

Hertford Office Park, Building I

90 Bekker Road, Vorna Valley

Midrand, Gauteng, 1682

Tel: 0800 110 200

8. REGISTRATION NUMBERS

DOTAREM: 31/28/0550

DOTAREM PREFILLED SYRINGES: 31/28/0551

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of registration: 1 September 1997

10. DATE OF REVISION OF THE TEXT

Date of revision: 3 November 2025